Inner Workings: Using vaccines to harness the immune system and fight drugs of abuse

Leah Shaffer, *Science Writer*

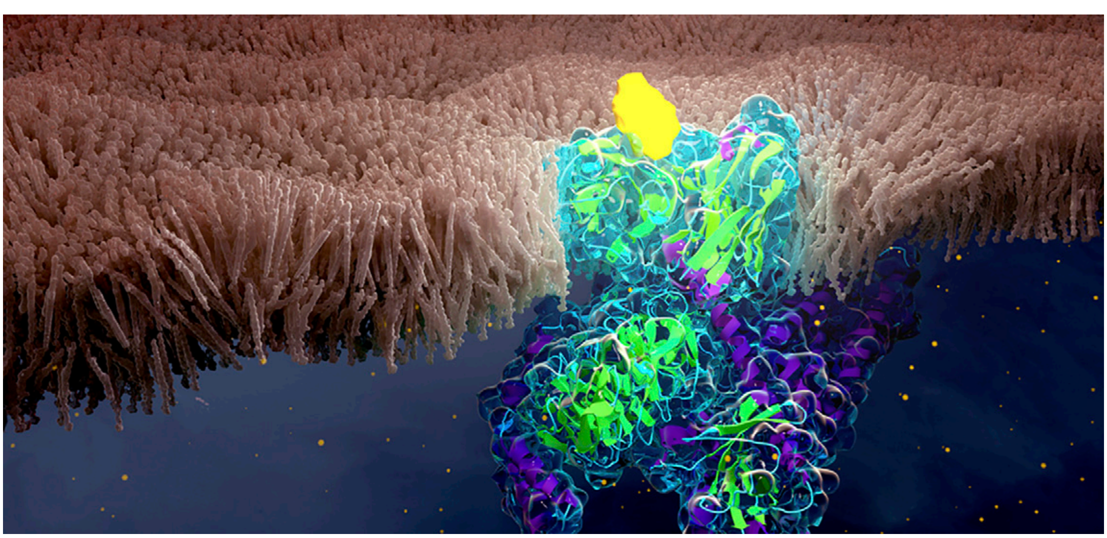
Opioids continue to ravage large swaths of the United States. Buffeted by social isolation, financial pressures, and limited mental health resources during the coronavirus disease 2019 (COVID-19) pandemic, addiction and its ill effects have only worsened in the past year. More than 100,000 people died from drug overdose between April 2020 and the end of April 2021, a roughly 30% increase in deaths compared with the previous year and an all-time high for the number of overdose deaths recorded in the United States. About three-quarters of those deaths resulted from synthetic opioid abuse.

And yet, few medical treatments are available for those experiencing opioid and other severe substance abuse disorders. Individuals addicted to opioids can wean off these drugs using methadone or buprenorphine, which offer opioid replacement—a safer variation of the drug that doesn't cause a high or lead to an overdose. And naltrexone, an opioid antagonist, blocks the opioid receptors. But these treatments have drawbacks and are not effective for everyone, especially long-term.

In the next few years, however, those seeking treatment may find help from a surprising source: their own immune system. Researchers are developing vaccines that would stimulate the production of antibodies to destroy opioid molecules before they ever reach the brain, thus blocking both the high and the potential for overdose. Right now, the first vaccine against opioid painkillers is working its way through early clinical trials at the New York State Psychiatric Institute.

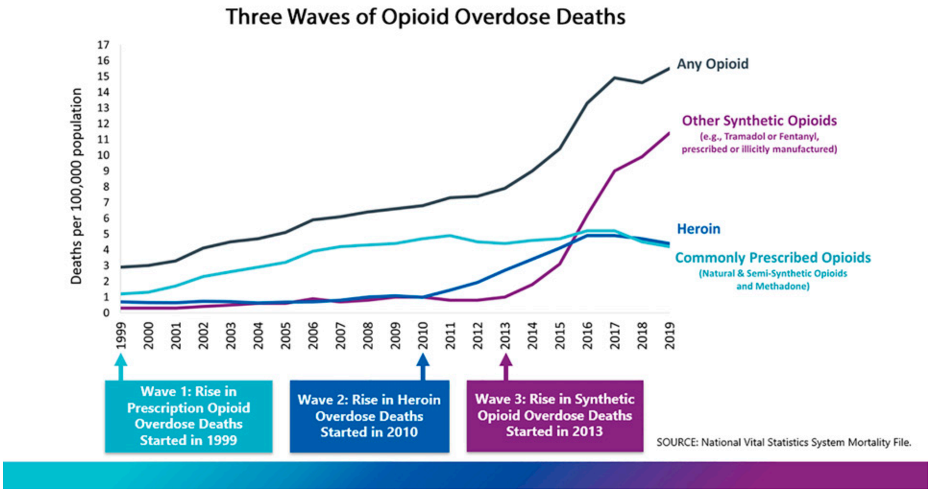
The idea of using vaccines against drugs of abuse has been around for decades—researchers initially targeted nicotine and cocaine. Thus far, research into these sorts of inoculations has seen little success. Nevertheless, the notion has started to attract attention in recent years; the NIH has been channeling funds into opioid vaccine research since 2018 through the HEAL Initiative (Helping to End Addiction Long-term). The infusion of grants has brought a much-needed boost to the field. And increased attention to vaccines owing to the pandemic—as well as interest in lab-engineered monoclonal antibodies—has buoyed the notion of vaccinating against addiction, perhaps making it a viable option in the foreseeable future.

Of course, a multitude of challenges remain, not all of which entail crafting a vaccine that effectively



One way to address opioid addiction is by using antibodies to destroy opioid molecules before they ever reach brain receptors, such as the mu-opioid receptor illustrated here. Image credit: Science Source/NANOCLUSTERING.

Published December 21, 2021.



The opioid epidemic has come in waves, ravaging large swaths of the United States. Image credit: Centers for Disease Control and Prevention, National Center for Injury Prevention and Control.

primes the immune system. The vaccine approach will only work in concert with counseling and behavioral changes. And ideally, multiple vaccines—or multivalent versions of a vaccine—would eventually be approved, so that desperate users can't just seek out a replacement drug.

Shot in the Arm

The Columbia University researchers leading the first opioid vaccine trial are administering the vaccine to patients with opioid use disorders to see whether they will develop antibodies against the oral painkillers oxycodone, oxymorphone, and hydrocodone. If the trial succeeds, a vaccine against heroin could soon follow, as well as immune system weapons against other drugs of abuse. The prospect is enticing: In principle, vaccine-induced antibodies would protect the patient from overdosing and experiencing a drug-induced high. The approach could allow the patient to ease off a drug while working long term to stymie a potential relapse.

"It would provide continued protection and hopefully we could re-engage the patient back into treatment," says Sandra Comer, a neurobiologist at New York State Psychiatric Institute and Columbia University Irving Medical Center, NY. "It's sort of like a safety net."

Comer and University of Minnesota (Minneapolis) associate professor of pharmacology and medicine Marco Pravetoni are in the midst of phase I clinical trials for their vaccine against oxycodone. Trial participants will have inpatient stays at a hospital over a couple of months, where they will receive the first three doses of the vaccine. The subjects will be monitored for a few months before returning to receive the fourth dose; the trial will test two different vaccine dose levels against placebo groups. Thus far, autoimmune reactions have not been a problem, at least according to Pravetoni's preclinical work.

Whether fighting drugs or microbes, the vaccine principle is essentially the same: Develop antibodies against the target. In the case of drugs of abuse, a small molecule is the target—but one that's often too small to be attacked by the immune system. So researchers craft the vaccines by chemically linking the opioid's small molecules to larger virus-like

Lethal doses of heroin, carfentanil, and fentanyl (*Left* to *Right*) equate to very different amounts. Image credit: United States Drug Enforcement Administration.

carrier proteins such as keyhole limpet hemocyanin (1). Along with linking the opioid antigen (called a hapten) to a larger particle, vaccine designers can add a variety of adjuvants—molecules serving as immune response amplifiers.

Different adjuvants have different advantages in vaccine design. For instance, in animal studies, researchers at Jay Evans' University of Montana, Missoula, lab found that linking the carrier particle in a vaccine to the adjuvants such as aluminum salts and toll-like receptors (TLR) was effective at increasing the immune response to fentanyl (2). TLRs attract pattern recognition receptors on immune cells, whereas aluminum salts help attract immune cells and serve as a depot to combine the carrier proteins into even bigger particles that will draw more attention from the immune system (3).

Essentially, these vaccines are designed to carry as many red flags as possible to spur the production of antibodies that will attack the small molecules of opioids. But finding the right mix of all these components is not easy. Vaccine effectiveness hinges on not only each individual's immune response but also a multitude of other factors including age, sex, amount of drug injected, whether the patient is taking different drugs concurrently with opioids, as well as the individual's genetic makeup.

Pravetoni's vaccine has been tested on mice, rats, dogs, and non-human primates, studies that all suggest that vaccine is safe and can reduce opioid distribution to the brain. But it's not easy to translate that to humans. In hopes of doing so, Comer's group will be scrutinizing biomarkers associated with the production of more antibodies. Researchers are keen to discover whether these proposed vaccines can produce enough antibodies to be effective across a broad population.

To determine effectiveness, researchers will have to gauge the oftentimes complex nature of the immune system response. Humans and most test animals have a stable of immune cells, called naïve or memory B cells, that are ready to respond to unfamiliar foreign molecules. After vaccination, these immune cells proliferate and produce antibodies that attack the threat. Different individuals have different amounts of the naïve B cells, which can determine just how robust the response can be. But in preclinical models, Pravetoni and colleagues found that before vaccination, mice displaying more naive memory B cells specific to oxycodone mounted a more effective antibody response against the drug after vaccination (4).

In the current trials, the team will be measuring this naïve B cell activity in patients before and after vaccine doses. If the effect seems to be robust and lasting, researchers could use that B cell production as a biomarker to target individuals who will respond best to the treatment, says Comer.

Comer is hoping to see the same thing that Pravetoni saw in mice—the people who show the strongest B cell activity before vaccination will also be the ones who show the strongest vaccine response.

Complicated Chemistry

The hurdles may be even higher for other drugs. In the 1990s and early 2000s, researchers struggled to design a vaccine against nicotine and cocaine. "It really depends on how the drug interacts with the body and the body interacts with the drug," says Kim Janda, professor of chemistry at Scripps Research Institute in La Jolla, CA.

The targeted drug's half-life, toxicity, dose size, and affinity for brain receptors can all factor into just how viable a vaccine can be. Success with a vaccine against one drug of abuse may not apply to others. "You can't just interchange parts that readily," Janda adds.

An oxycodone vaccine may not stimulate enough antibody production, says Janda, to overcome the affinity those drugs have for receptors in the brain. He believes an easier target with antibodies is fentanyl and its analogues such as carfentanil—synthetic opioids that are responsible for the highest number of opioid deaths yearly because of their potency. That same potency makes the drug easier to target with a vaccine; since synthetic opioids only need to enter the body in much smaller doses, it takes fewer antibodies to overwhelm it. Plus, the synthetic opioids have shorter half-lives than heroin or the pain pills, which means the antibodies have a better chance of wiping the drug out before it reaches the brain.

Engineering Antibodies

There may be some advantages, however, to relying not on the antibodies generated by a person's immune system but instead on antibodies engineered by clinicians. Manufactured in the lab, monoclonal antibodies (mAbs) have a big advantage over vaccine-produced antibodies: They work right away, rather than in weeks or months. Janda wants to use the mAB approach for fentanyl and possibly heroin addiction (5).

In contrast to a vaccine, these antibodies can be engineered to hit more specific drug targets, and the dose can be tailored to the amount of drug intoxication. Typically, mAbs have been used in cancer treatment with a steep price tag. But production and engineering advances, as well as increased use of antibodies during the pandemic, have brought prices down somewhat (6).

> **"We envision a patient being given, for example, methadone treatment, but still getting the vaccine in anticipation of their release from the clinic."**
>
> **–Marco Pravetoni**

Even so, mAbs are not cheap. Pravetoni suggests that in the near term, they could be used on a limited basis for certain high-risk populations, in combination with other treatments. That could, for example, include members of the military, who could be exposed to synthetic opioids in a chemical attack. This scenario is not purely hypothetical. In 2002, Russians used aerosolized synthetic opioids to subdue

https://doi.org/10.1073/pnas.2121094118

terrorists holding hostages; they ended up killing more than 100 of those hostages who experienced ill effects while knocked out by the drug.

Pravetoni adds that their vaccine could also be paired with existing treatments—it won't interfere with treatment opioids like methadone. "We envision a patient being given, for example, methadone treatment, but still getting the vaccine in anticipation of their release from the clinic," says Pravetoni.

New Targets, Next Steps

Janda and others are working on immune therapies against methamphetamine and cocaine as well. Both targets figure to be quite tricky. In the case of meth, its simple structure resembles that of an amino acid; hence, any immune response has to be very specific to the drug's molecules so that the immune system doesn't attack the body's own amino acids. "Trying to get an immune response to something that looks like an amino acid is not easy," he says.

Tinkering with the vaccine components *could* point to a solution. For meth, researchers may need to redesign the hapten, the piece of the small molecule that connects to a carrier protein. There are similar challenges inherent in designing antibodies or vaccines against cocaine (7), efforts that remain in the preclinical stages.

Janda is less confident in using vaccines to target nicotine, having seen many failed trials in the past three decades. In previous attempts, the vaccine did not consistently generate enough antibodies to effectively attack the amount of nicotine circulating in the system. Comer also has her doubts—she's seen too much variability in antibody generation amongst different individuals, she says.

But enlisting the immune system to fight opioids may show promise. With years of experience in tinkering with and manufacturing vaccine components, if the painkiller vaccine is approved, "we are poised to accelerate that process for other vaccines," says Pravetoni.

The coming years could see a variety of treatments—and that's certainly a good thing. Like most disorders, addiction can't be tackled with a lone silver bullet. Hypertension and diabetes take multiple interventions, Pravetoni notes. "Why," he asks, "can't we do this with addiction?"

1 M. D. Raleigh *et al.*, Opioid dose- and route-dependent efficacy of oxycodone and heroin vaccines in rats. *J. Pharmacol. Exp. Ther.* **365**, 346–353 (2018).

2 S.M. Miller *et al.*, A novel TLR adjuvant increases the efficacy of vaccines against fentanyl-induced toxicity and overdose. *J. Immunol.* **204** (suppl.1), 91.25 (2020).

3 M. E. Olson, K. D. Janda, Vaccines to combat the opioid crisis: Vaccines that prevent opioids and other substances of abuse from entering the brain could effectively treat addiction and abuse. *EMBO Rep.* **19**, 5–9 (2018).

4 M. Laudenbach *et al.*, The frequency of naive and early-activated hapten-specific B cell subsets dictates the efficacy of a therapeutic vaccine against prescription opioid abuse. *J. Immunol.* **194**, 5926–5936 (2015).

5 L. C. Smith *et al.*, Monoclonal antibodies for combating synthetic opioid intoxication. *J. Am. Chem. Soc.* **141**, 10489–10503 (2019).

6 S. Pecetta, O. Finco, A. Seubert, Quantum leap of monoclonal antibody (mAb) discovery and development in the COVID-19 era. *Semin. Immunol.* **50**, 101427 (2020).

7 K. C. Collins, J. E. Schlosburg, P. T. Bremer, K. D. Janda, Methamphetamine vaccines: Improvement through hapten design. *J. Med. Chem.* **59**, 3878–3885 (2016).